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Part IV

Department of Health, Education, and Welfare

National Institutes of Health

Program to Assess the Risks of Recombinant DNA Research; Final Plan

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

Recombinant DNA Research; Final Plan For a Program To Assess the Risks of Recombinant DNA Research

AGENCY: National Institutes of Health.

ACTION: Notice of final plan for a program to assess the risks of recombinant DNA research.

SUMMARY: This notice sets forth the final plan for the first annual NIH program to assess the risks of recombinant DNA research.

EFFECTIVE DATE: September 13, 1979.

FOR FURTHER INFORMATION CONTACT: Additional information may be obtained from Dr. John Nutter, Chief, Office of Specialized Research and Facilities, NIAID, National Institutes of Health, Bethesda, Maryland 20205 (301–496–5643).

SUPPLEMENTAL INFORMATION:

A. Decision of the NIH Director to issue the Final Plan.

I. The Proposed Plan was published in the **Federal Register**, Vol. 44, No. 64, Monday, April 2, 1979, pages 19302 to 19304. Following one extension, a formal closing date for Public Comment of June 2, 1979 was established. Thirteen correspondents submitted comments on the plan and they were divided into four generic categories as follows:

(1) *Opposition to the Program.* One correspondent noted that there is far less public and scientific concern today regarding DNA technology than there has been in prior years. Risk assessment studies were characterized as being costly and time consuming, diverting responsible scientists from research activities and being of questionable and limited probative value. Additionally he noted that there exists no definitive evidence of risk associated with any research involving recombinant organisms or products isolated from such organisms.

I am required to establish that actions under the NIH Guidelines for Recombinant DNA Research present no significant risks to health or the environment. Furthermore, to the maximum extent possible, these judgments should be based on a foundation of documented research that is subject to peer review. While I concur with most scientists that the perception of risk from this research is certainly less now than earlier, there still remain selected areas where data are insufficient to determine risk. This final plan is an attempt to satisfy this remaining need and will afford an opportunity to assess progress toward achieving the scientific objectives at least annually.

In response to other concerns of this correspondent it should be noted that the Special Assistant for Risk Assessment, NIAID does not have authority to make rulings superseding the Guidelines, nor will he function in a preliminary review role for submissions to the Recombinant DNA Advisory Committee (RAC). He/she will, as specified in the Plan, provide scientific leadership, aid in the interpretation of data from diverse sources and be the focus for the interaction of the Risk Assessment Program with the RAC.

(2) *Criticism of supporting statements.* Three correspondents criticized the interpretation of recent risk assessment experiments involving polyoma virus (see also RAC section below). The controversy seems to be essentially centered on the concluding sentence in the second paragraph of section II of the Proposed Plan; "In each case, there was no evidence that the inserted DNA produced any special hazard." It should be said that this experiment was performed by NIH scientists at the request of RAC and was conducted under P4 conditions; these circumstances limit the number of experimental variables that can be completed within a reasonable time. Accordingly, the protocols were reviewed widely by virologists before the studies were initiated.

Since one of the initial concerns related to the potential for the delivery of recombinant DNA molecules to mammalian cells by prokaryotic hosts attention was focused on that model. We have again reviewed all available data in the light of the criticisms received. We conclude that in the polyoma virus risk assessment experiments, potentially infectious or tumorigenic recombinant DNA molecules were not transferred out of EK2 hosts into susceptible mouse or hamster cells to produce either progeny virions or tumors. We have altered the wording in the Final Plan to reflect this conclusion.

(3) *Support and General Suggestions for the Program.* Four correspondents submitted letters supporting the Proposed Plan as published and made general suggestions for improving its effectiveness and impact.

Both the Proposed and Final Plan indicate that the Special Assistant for Risk Assessment will represent the Plan to the RAC. The Special Assistant will be a member of NIAID, the Institute with programmatic responsibility. RAC will, in its advisory capacity, continue to have a major impact on the constitution of the relevant programs. We envision the Special Assistant reporting progress to the RAC at its meetings and the Committee will review each annual updated Plan.

The importance of considering issues and synthesizing information in conferences and workshops was noted. We recognize the beneficial impact of this approach for identifying both problems and solutions and the Plan affords both the leadership and support for such activities. One area for such an approach is the question of autoimmune responses and this is included in the Plan along with other topics under Prokaryotic Host-Vector Systems. Additional areas may be added as a result of RAC advice and the interaction of the Special Assistant with the scientific community and interested public groups.

Encouragement to extend the specific studies on prokaryotic host-vector systems to *Bacillus subtilis* was received. The NIAID will seek the advice of RAC, through its Risk Assessment Sub-Committee, for suggested studies and other aspects of this plan. The proper emphasis and level of integration of *B. subtilis* studies with those based on *E. coli* will be a subject for discussion with that group.

One correspondent suggested the support of "worst-possible case" experiments by the NIH in maximum containment laboratories in order to reveal the maximum magnitude of the hazards. The Plan indicates that the NIH has facilities appropriate for the conduct of such studies and we anticipate continuing to maintain such laboratories in a state of readiness. Therefore, if the NIH receives requests for facility support or advice from RAC to perform directly such experiments the capacity to do the work will exist.

(4) Specific suggestions related to personal research interests.

Five individuals submitted statements indicating the relationship of their research to the various areas indicated in the Proposed Plan. Most of these comments suggested biological approaches or experiments that fall within the Plan's areas of scientific interest. Areas indicated were: ecological studies employing novel tracing techniques of the host strains, transfer of genetic information between unrelated bacteria, new approaches to the study of *E. coli* colonization of laboratory animals, and a suggested protein of biological importance for inclusion in studies of prolonged colonization.

While these suggestions are relevant to risk assessment studies they fall within the broad area of research supported through the regular grants program and should be incorporated into applications for such support. When specific research activities are requested by NIH for support through the grant or contract mechanism, the solicitations will be widely publicized in the NIH Guide for Grants and Contracts and in the Commerce Business Daily. Correspondents will then have the opportunity to make application if their interests lie within the area of solicitation.

One submission was received that addressed issues outside the Proposed Plan. This correspondent expressed an interest in pursuing research on some specific societal implications of recombinant DNA research. This general area was also supported in a less specific manner by one of the commenters cited in paragraph (3) above. This correspondent is urged to seek funding through the regular grants channels of the several agencies supporting research on Recombinant DNA Molecules.

II. The Recombinant DNA Advisory Committee considered the Proposed Plan at its Meeting on May 21, 1979. Dr. Richard M. Krause, Director NIAID presented a summary of the program and responded to questions.

Members of the public were provided an opportunity to address the committee and present their views about the proposed program. Comments were approximately equally divided between suggested areas to be added and criticisms of the interpretation of the polyoma risk assessment experiments cited in the Proposed Plan as background information. Suggested additions were to monitor nosocomial infections, monitor transfer from laboratory to wild type strains, and expand research on the role of plasmids and phages in the etiology of diseases.

Members of the Risk Assessment Sub-Committee of the RAC commented on the Proposed Plan and other committee members were provided opportunity to comment and ask questions. The Scientific Aspects and Implementation sections were received without significant criticism and the RAC did not recommend changes in regard to other issues which were raised by the public. The final Plan will permit close cooperation between the Program constituents and the RAC. As a first step the NIAID will work with the Risk Assessment Sub-Committee in developing areas that require risk assessment projects. NIAID will develop a plan for the orderly implementation of those projects of greatest importance.

B. Final Plan for a Program To Assess the Risks of Recombinant DNA Research

I. Introduction

With the issuance in December 1978 of revised guidelines for the conduct of recombinant DNA research, the Secretary DHEW requested that the National Institutes of Health (NIH) prepare an NIH Risk Assessment Plan, which after review by the Recombinant DNA Advisory Committee (RAC) and publication in the **Federal Register** for comment, would be made final and updated annually. The present document is the response to that request.

The major concerns about recombinant DNA experimentation have included the possible converson of non-pathogenic microorganisms to pathogenic agents, as well as the establishment of organisms containing recombinant DNA molecules in the ecosystem. Since the hypothetical risks and technical basis of recombinant DNA research are primarily microbiological in nature, the responsibility for coordination and implementation of the plan was assigned by the Director, NIH to the Director, National Institute of Allergy and Infectious Diseases (NIAID).

The vast majority of information relevant to recombinant DNA risk analysis has already come from research not primarily designed to provide information on risk. This will undoubtedly continue to be the case. This information will be obtained chiefly from publications in the scientific literature, from persons with special scientific knowledge, and from ongoing basic biomedical research. Risk assessment analysis will require continuing review of data developed in the fields of microbiology, infectious diseases, and related biological research.

Some essential information has been, and will continue to be, derived from projects specifically designed to assess various aspects of potential risks associated with recombinant DNA experimentation. Such experiments will be supported by the Intramural and the Extramural programs of NIH. Many experiments may also be conducted in the private sector or may be funded by other agencies or governments.

The essential goal of a successful risk assessment plan will be the development of means to collect, collate, coordinate, evaluate, and disseminate data obtained from all sources.

II. Background and Present Program

The revision of the guidelines for recombinant DNA research was developed primarily through the analysis of data generated from basic microbiological research, such as was done at the Falmouth and Ascot Risk Assessment Workshops. An example of such free-ranging research efforts which have generated data relevant to recombinant DNA experimentation was the discovery of the intervening sequences that interrupt genes in eukaryotic DNA. This finding virtually assures that shotgun cloning of eukaryotic chromosomal DNA into prokaryotes will not result in the production of biologically active proteins.

Special experiments have been and will continue to be specifically designed to assess the potential risks associated with recombinant DNA experiments. For example, within the Intramural Program of NIAID two experiments were undertaken to assess potential risks of this new technology. The first was an evaluation of the infectivity of polyoma DNA when the entire viral genome was cloned in phage and plasmid vectors of *Escherichia coli* K–12. A second experiment was a study of the pathogenicity and stability of shotgun clones of *E. coli* K–12 containing yeast (*Saccharomyces*) DNA. In the polyoma virus risk assessment experiments, potentially infectious or tumorigenic recombinant DNA molecules were not transferred out of EK2 hosts into susceptible mouse or hamster cells to produce either progeny virions or tumors. In the second experimental model there was no evidence that the inserted DNA produced any special hazard.

Specific risk assessment experiments have also been undertaken using the NIH contract mechanism. Contracts have been used to (1) assess the potential for generating aerosols in laboratories where recombinant DNA research is conducted and (2) to examine the EK2 systems for their ability to survive and their capacity to transfer heterologous cloned segments to secondary hosts under conditions simulating natural environments.

An important additional source of information is specific DNA risk assessment experiments that have been undertaken in foreign countries. Scientists supported by the European Molecular Biology Organization (EMBO) have also examined the infectivity of recombinant polyoma plasmid and phage DNA in tissue culture. The results of these studies agree with those of biological *in vivo* assays carried out by

the Intramural scientists of NIH already described.

III. Recombinant DNA Risk Assessment Plan: Scientific Aspects

There are threee major types of host-vector systems presently being used for recombinant DNA research, and the risk assessment program will naturally be focused on these. They are (1) prokaryotic host-vector systems, primarily, *E. coli* and *Bacillus subtilis;* (2) lower eukaryotes, namely, *Saccharomyces cerevisiae* and *Neurospora crassa;* and (3) eukaryotic viruses in cultured cells of higher eukaryotes.

A number of events must occur before a laboratory microorganism becomes a possible risk to people or higher organisms outside the immediate laboratory environment. The assessment of risk involves a determination of the probability for the occurrence of these various events. The particular data that are most susceptible to analysis, or most likely to provide a definitive answer concerning risk, will differ for the various host-vector systems. Data elements will include the probabilities of:

(1) Dispersal of the organism containing recombinant DNA into the environment.

(2) Survival of the organism in the environment or transfer of the recombinant molecule into another organism.

(3) Acquisition of a selective advantage by the recombinant-containing organism so that it can populate a significant ecological niche.

(4) Change in the natural biology of the recombinant-containing organism so that it becomes a danger to some higher organism, as, for example, by its conversion into a pathogen or into a vehicle for transferring foreign DNA into cells of the higher organism.

A major aspect of the risk assessment plan will consist of acquiring and analyzing information and data relevant on these elements for the various host-vector systems.

The following compilation of research activities in neither final nor inclusive. Furthermore, those mentioned here will require more than a single year to complete. While the present interest emphasizes *E. coli* host-vector systems in animals, in the near future the focus may shift to other host-vector combinations and their impact on the ecosystem.

Prokaryotic Host-Vector Systems

With regard to acquisition of new experimental data, the initial emphasis will be on the *E. coli* K–12 systems, since these are the major systems being used and areas where such data are needed have already been identified. The following areas will be given particular consideration.

(1) The survival in the environment and potential selective advantage of organisms carrying recombinant DNA.

(2) Further evaluation of the transmission of vectors from *E. coli* K–12 to other bacteria in the gastrointestinal tract of animals and human beings.

(3) Testing *E. coli* K–12 host-vector systems carrying recombinant DNA for virulence or increased ability to colonize the gastrointestinal tract of mice.

(4) Animal studies of hormone-producing strains of *E. coli* generated by recombinant DNA technology.

(5) Further evaluation of the biological activity of polyoma virus cloned in *E. coli* host-vector systems.

(6) The biological activity of *E. coli* K–12 clones carrying DNA copies of RNA tumor viruses.

(7) The possible occurrence of autoantibodies or autoreactive cells due to the production of eukaryotic polypeptides by bacteria that colonize higher organisms.

Lower Eukaryotes

Areas where new experimental data would be desirable include (1) determining the competitive advantage for survival of *S. cerevisiae* in relevant natural environments and (2) determining the ability of several types of eukaryotic viruses to replicate in *S. cerevisiae* and *N. crassa* when introduced via a recombinant molecule.

Higher Eukaryotes

The major concern that centers on the use of animal virus vectors to clone foreign DNA segments in cells of higher eukaryotes involves the unlikely possibility of (1) creating novel nondefective viruses as a result of the insertion of a new DNA fragment or (2) altering the host range of the viral vector. The risks associated with these problems will be evaluated continuously through the review of the general viral literature. Only a limited number of experiments are currently being conducted with these systems and it is highly improbable that the events enumerated above would occur. Specific risk assessment experiments are not being planned at present for these systems.

IV. *Implementation of Plan*

In order to implement the plan, NIAID will:

(1) Recruit and appoint an eminent scientist as a Special Assistant to the Director for Risk Assessment to provide leadership and coordination of all activities concerned with the evaluation of risks of research and research products related to recombinant DNA and other genetic research involving potentially infectious or toxic organisms. In this role, this scientist will be responsible for representing the plan to the Recombinant DNA Advisory Committee (RAC), the scientific community, international organizations, and the public; will advise on the collection and assessment of data and edit and coordinate reports on progress; and will chair workshops and conferences as necessary to address special problems of risk assessment. This individual will also review ongoing research for data pertinent to risk assessment by such means as analysis of data from research which is published or presented at meetings, by direct contacts with scientists, and through review of Memoranda of Understanding and Agreement (MUAs) filed with the Office of Recombinant DNA Activities (ORDA). Liaison will be maintained with those who have related responsibilities in other countries and international scientific organizations. The Institute will recruit and appoint such ancillary staff as are needed by the Special Assistant.

(2) Develop and issue such requests for applications or proposals as are necessary to ensure the conduct of risk assessment research required to answer specific questions or to fill gaps in data being accumulated from other research. It is anticipated that these specific needs will be identified by the activities of the Special Assistant for Risk Assessment, the RAC, and scientists addressing the issues in workshops and conferences.

(3) Prepare and send periodic reports to the RAC identifying questions, problems, and evaluations of scientific information pertinent to their various advisory functions.

(4) Respond to inquiries from scientists, the public, DHEW, or other government agencies regarding available data on risk assessment and evaluation of those data.

In order to carry out these responsibilities, the NIAID will enlist the services of the following existing NIH offices, committees, and people to provide information, to advise and evaluate, and to review, as appropriate, reports for completeness and accuracy.

(1) Recombinant DNA Advisory Committee (RAC)

A Risk Assessment Subcommittee has recently been established in the RAC to provide the NIH with broad technical and public policy advice concerning risk assessment. This subcommittee will

serve as the focus for RAC advice and interaction with the various program elements.

(2) Office of Recombinant DNA Activities (ORDA)

ORDA will maintain a registry of ongoing recombinant DNA research as filed in MUAs. The registry, which will include information on hosts, vectors, sources of inserted DNA, containment levels, etc., will serve as a resource for information on ongoing research which can be reviewed for risk assessment aspects.

(3) Office of Specialized Research and Facilities (OSRF)

The OSRF will:

(a) Manage grants and contracts solicited as a result of program efforts.

(b) Serve as a clearinghouse for special facilities, services, and other resources required by the plan.

(c) Organize workshops and conferences as necessary to evaluate research or coordinate these efforts.

(d) Maintain contact for information exchange with international groups conducting or fostering risk assessment work.

(e) Serve as central office for data compilation.

(4) Intramural Scientists

The NIH had available high containment laboratories which will provide a long-range base for risk assessment experiments requiring such technology. Intramural scientists in NIAID and other NIH laboratories will also contribute pertinent information and will serve as ad hoc consultants on the various aspects of risk assessment.

(5) NIH Extramural Program Officers and Executive Secretaries of the Study Sections

These individuals will serve as a valuable resource because of their familiarity with grants and contracts covering a full range of scientific disciplines supported by NIH which may yield valuable risk assessment information.

Dated: September 5, 1979.

Donald S. Fredrickson,

Director, National Institutes of Health.

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